








Research Article

Diagnosis and Prognosis in Disorders of Consciousness: An Active Paradigm fMRI Study

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Diagnoses in patients with disorders of consciousness are prone to misdiagnosis; thus, research has sought approaches to increase reliability, for instance, with functional MRI. By applying a motor imagery task, patients showing covert command following despite the absence of behavioural signs of awareness can be identified as being in a cognitive motor dissociation. This study seeks to determine the proportion of patients, with unresponsive wakefulness syndrome and minimally conscious state, who display covert command following. Moreover, the prognostic value of the improved diagnosis and different methodical approaches to analyse the functional MRI data were evaluated. 73 disorder of consciousness patients (35 unresponsive, 35 minimally conscious, and three already recovered) underwent weekly standardized behavioural assessments with the coma-recovery scale—revised and one functional MRI examination comparing their brain activations in the supplementary motor area between phases of imaging playing tennis and rest. 27 healthy controls served as a control group. The data was evaluated using different region-of-interest analyses (one- and two-tailed small-volume correction and region-of-interest exploration approaches) and a whole-brain analysis. Based on the one-tailed small volume correction data, seven patients, all of nontraumatic aetiology, showed covert command following. The one-tailed region-of-interest exploration identified three additional responders. 10 patients showed significantly more activation during rest than during the imagery paradigm (negative responders). 40% of patients (minimally conscious patients being three times more likely) showed significant activations in the whole brain analysis. Besides, no significant further associations were found between covert command following and clinical parameters. The analyses showed that the tennis paradigm could identify patients with cognitive motor dissociation with a nontraumatic aetiology, but our data failed to show any short-term prognostic validity. The relevance of negative responders and activated regions outside of the region of interest should be further investigated.

1. Introduction

The term disorders of consciousness (DoC) includes the pathological states of coma [1], unresponsive wakefulness syndrome (UWS [2], formerly vegetative state [3] or apallic syndrome [4]), and minimally conscious state (MCS) [5]. MCS has also been subcategorized into MCS+ and MCS- based on the complexity of the behavioural responses of the patient (for example command following vs. minimal behavioural interaction) [6]. Confusional state [7] is often misdiagnosed as being DoC but is, per definition, a conscious state. DoC are most often caused by traumatic injuries or cardiovascular failure, but also by progressive degenerative [8] or metabolic diseases [9]. DoC are primarily diagnosed by observing a patient's behaviour but are prone to misdiagnosis, especially if examiners solely rely on unstructured clinical bedside testing [10]. Besides using standardized tests like the coma recovery scale-revised (CRS-R [11]), functional MRI (fMRI) and EEG have been used increasingly to make diagnosis more reliable and are also recommended by the guidelines of the European Academy of Neurology [12].

Cognitive motor dissociation (CMD) [13] is also known as functional locked-in-syndrome [6] or covert awareness [14]; a consensus on the name is not yet found [15]. The terms apply for DoC patients who lack behavioural signs of consciousness but show neuronal responses to different types of neuroimaging [16–18] as well as electrophysiological paradigms [19, 20]. As a consequence of these newly detected neuronal capacities, a patient who was behaviourally diagnosed as UWS or MCS- but shows CMD can then be rightly classified as MCS+. In CMD, the connectivity between subcortical and cortical areas is impaired [21] in contrast to patients suffering from classical locked-in syndrome where the main locus of injury is the ventral pons [22–24]. Studies found that in patients suffering from acute [25] and chronic [16] brain injury, the prevalence of CMD is around 14–15%. A meta-analysis revealed that the prevalence of preserved consciousness is comparatively low in patients with UWS but doubles in MCS patients and appears more often in traumatic compared to nontraumatic brain injury [16].

In 2006, Owen et al. introduced active fMRI paradigms [26–29]. The patients were instructed to imagine navigating through familiar places and playing tennis, and some were able to wilfully modulate their brain activity in the same way as healthy controls, even when no command following could be observed at the bedside.

Concerning prognosis, first studies show that if CMD is found in patients with an acute [25] or prolonged [30] DoC, they made greater behavioural progress at a three- [30] and 12-months [25] follow-up than those without CMD.

In this study, we utilize the active motor imagery tennis paradigm, exploring different ways of analysing fMRI data and investigating the relevance of CMD to improve the diagnostic and prognostic utility in DoC patients.

2. Materials and Methods

2.1. Aims. This retrospective study is aimed not only at reexamining previous findings of diagnostic and prognostic

DoC research but also at extending them by using different analysis methods on one of the currently largest fMRI datasets in the field.

Using a region-of-interest (ROI) analysis approach, two research questions are addressed: firstly, whether the tennis paradigm can improve the diagnosis of DoC by revealing patients who were misdiagnosed on the sole basis of behavioural tests and, secondly, whether the diagnosis of DoC with and without CMD has a short-term prognostic value by comparing the improvement of the revealed CMD patients to patients who showed no CMD. To answer the diagnostic research question, the proportion of patients with DoC who show covert command following (CCF) is first determined, which is indicative of CMD. Response rates will be compared between different types of ROI analysis to draw conclusions about their sensitivity to identify CMD patients. The hypothesis, that activation in the ROI is higher during the active phase of the paradigm than during rest and, more generally, that the strength of activation differs, is tested. Associations between the presence of significant activation in the ROI during motor imagery and clinical variables are investigated exploratively. For the prognostic effect, the improvement of the level of consciousness of DoC patients with and without CMD at the time of discharge from the hospital is investigated. This prognostic assumption will be tested for its predictive power in comparison to clinical parameters.

Furthermore, an explorative whole-brain analysis (WBA) will be conducted across all DoC patients in the tennis paradigm to identify brain regions outside the ROI that also show significant activations. Thus, it can be determined whether and which further brain regions were activated and the frequency thereof.

2.2. Subjects. 73 patients (25 women) who suffered from DoC and received an fMRI scan including the tennis paradigm were identified at the Department of Neurology, Neurological Intensive Care and Neurorehabilitation, Christian Doppler University Hospital, between 2010 and May 2022. Patients who received no fMRI scan due to MRI incompatible implants (e.g., heart pacemaker), comorbidities (e.g., fulminant spastic syndrome), or excessive body movements interfering with the fMRI recording and those who received medication affecting the vigilance could not be included. The fMRI was part of the routine medical diagnostic procedure and the number of patients who could be included determined the sample size.

Moreover, 27 healthy controls (12 women) who were at least 18 years old were recruited and provided consent to participate in the study. Exclusion criteria for the healthy controls were nonremovable ferromagnetic or electronic body implants and a history of psychiatric or neurological disorders. Healthy controls and DoC patients who have fully recovered consciousness according to the CRS-R at the time of the fMRI examination served as control groups to evaluate the functioning and robustness of the tennis paradigm.

2.3. fMRI Paradigm. The tennis paradigm is based on the procedure used by Owen et al. [27] and Monti et al. [26] and was slightly adapted over the 12 years of data collection.

For the first eight years (until 2018, $n = 54$ patients), seven blocks of imaging playing tennis alternated with seven blocks in which subjects were supposed to relax (rest blocks). Before each block, an 8-second German instruction was given which instructed the patient to imagine playing tennis. Each block lasted 30 seconds. In 2019, the navigation block was introduced additionally ($n = 19$ patients, 27 controls). Since then, five alternating blocks of tennis, navigation, and rest phases, each of which now lasted 20 seconds, were conducted. The respective 8-second instruction did not change for the tennis and rest paradigm. In the navigation blocks, participants were instructed to imagine walking through the rooms of their own homes. However, this block is not analyzed in this paper since the focus is on the tennis paradigm. Throughout the 12 years, the auditive instructions were presented to the participants using pneumatic headphones and the Presentation® software of Neurobehavioural Systems (23.0, 2004).

2.4. Behavioural Assessment. DoC patients were routinely assessed behaviourally once a week by a trained neuropsychologist using the CRS-R [11]. The patients' diagnosis and total score at the time of the fMRI examination and their last CRS-R score and diagnosis before discharge were considered in the statistical analysis.

2.5. fMRI Data Acquisition. A three Tesla Siemens Tim Trio scanner (Siemens, Erlangen, Germany) was used to obtain structural and functional images during the study tasks in all DoC patients before 2018 ($n = 51$ patients), and a three Tesla Siemens Magnetom Prisma (Siemens, Erlangen, Germany) scanner was used for all patients and controls from 2018 onwards ($n = 22$ patients, 27 controls). Both were equipped with a 20-channel head coil and recorded 506 (Prisma) and 232 (Tim Trio) scans for each subject during the CCF paradigm. The first six scans were dummy scans and, thus, discarded. While the high-resolution structural scans were acquired with a T1-weighted standard MPRAGE sequence (Magnetom Prisma: 208 slices, slice thickness = 0.8 mm, time of repetition (TR) = 2400 ms, time-to-echo (TE) = 2.24 ms, field-of-view (FOV) = 256 mm, flip-angle (FA) = 8°; Tim Trio: 160 slices, slice thickness = 1.2 mm, TR = 2300 ms, TE = 2.94 ms, FA = 9°, FOV = 256 mm), the functional scans were conducted with a T2*-weighted gradient echoplanar-imaging (EPI) sequence. For the Tim Trio scanner, the functional scans consisted of 36 slices (slice thickness = 3 mm, TR = 2270 ms, TE = 30 ms, FA = 80°, FOV = 192 mm) and, for the Magnetom Prisma scanner, 56 slices (slice thickness = 2.4 mm, TR = 1050 ms, TE = 32 ms, FA = 45°, FOV = 192 mm). The adaption of the paradigm did not change the scanner settings.

2.6. fMRI Data Analysis. For the analysis of the fMRI data, version 12 of the software Statistical Parametric Mapping [31] (SPM) was used, implemented in the MATLAB R2013a program [32]. SPM was also used to create Figure 1, and labelling was added. Preprocessing started with head motion correction via the SPM realignment and unwarped function (registering all images to the first and

reslicing with 6th degree B-spline), followed by slice timing correction and linear normalization of the EPI images to the Montreal Neurological Institute (MNI) standard space EPI template in SPM12. Afterwards, functional data was smoothed with a 6 mm full width at half maximum Gaussian kernel, and finally, an independent component analysis-based strategy for automatic removal of motion artefacts (ICA-AROMA) [33] using nonaggressive denoising was applied. Afterwards, a general linear model was conducted for each voxel in order to model the fMRI time series (consisting of the two conditions tennis and instruction) as with a synthetic hemodynamic response function and AR(1) correction and a 128 sec high-pass filter for low-frequency drifts.

2.7. Different fMRI Analysis Strategies

2.7.1. ROI. The supplementary motor area (SMA) was defined as ROI based on the approach of Monti et al. [26], and a corresponding binary mask was created in SPM12 (centre at 0-4 57, consisting of 1079 voxels (at a $3 \times 3 \times 3$ mm resolution = 29133 mm³ volume (see Figure A1 in the supplementary material). This leads to a lower loss of statistical power due to its restriction to a small area of the brain, as correction of multiple comparisons must be applied when testing for contrasts [34].

Two different types of ROI analysis were conducted: a small volume correction (SVC) analysis and a ROI exploration analysis using the REX-toolbox [35]. For the SVC approach, a one-tailed t -contrast: tennis > rest and a two-tailed F -contrast: tennis vs. rest were conducted to compare different approaches. The respective contrasts were created for each subject individually and tested for significance. In both analyses, a cluster-level threshold of $p < .05$ (family-wise error-corrected for multiple comparisons) was used, while at the voxel level, an initial cluster-forming threshold of $p < .001$, uncorrected, was applied).

The contrasts in the ROI exploration analysis were not performed for each voxel in the ROI individually but on an average over all voxels in the SMA. Again, a one- and a two-tailed analysis were conducted. The resulting t values ≥ 1.67 (one tailed) and ≤ -1.96 or ≥ 1.96 (two-tailed) were defined as statistically significant.

Potential differences between the approaches can be identified. As the ROI exploration analysis uses the averaged contrast, only one statistical test has to be done, which, compared to the multiple testing approach of the SVC analysis, lowers the threshold for significance and improves sensitivity. However, if only few voxels within the ROI show activity, the ROI exploration approach could miss them due to averaging, which would suggest a higher sensitivity for the SVC approach.

2.7.2. WBA. An explorative WBA was conducted to identify further brain regions outside of the SMA that are significantly more activated during the tennis paradigm. The WBA was also conducted with SPM12 in MATLAB 2013a and was based on the same one-tailed t -contrast already used for the ROI (tennis > rest). The significance threshold

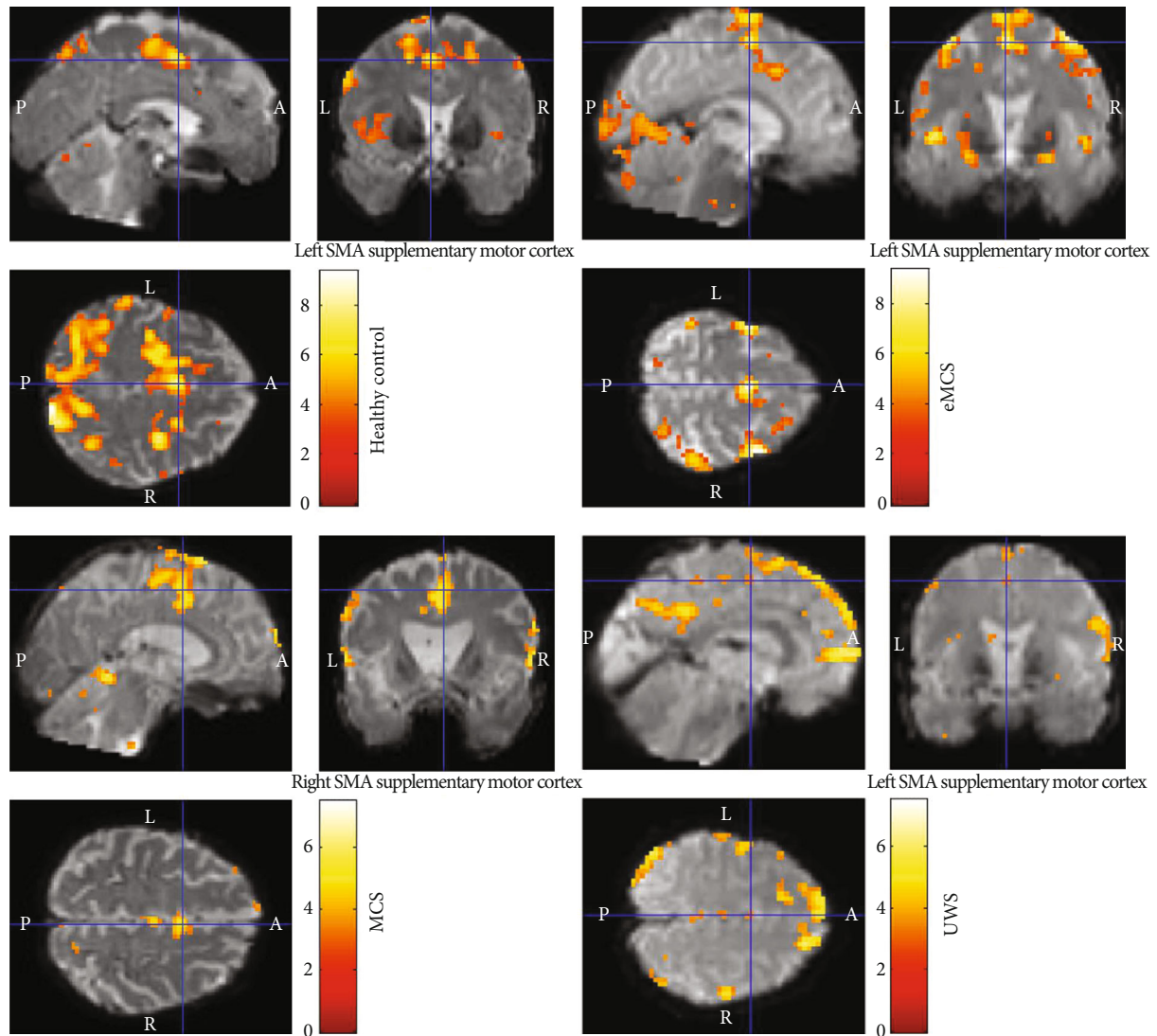


FIGURE 1: Activated brain regions during the tennis paradigm in all four subject subgroups: in all depicted responders, the activation of the SMA measured by functional MRI was significantly higher during tennis than during rest periods ($p < .001$, uncorrected). The colour bars indicate the t values of activations, and their scaling varies between control (0-8) and patient responders (0-6). The healthy control is subject at 26, the eMCS patient with ID 28, the MCS- patient with ID 72, and the UWS patient with ID 2. White letters indicate the spatial orientations: A = anterior; L = left; P = posterior; R = right. The blue coordinate cross in each of the four individual scans marks the position of the SMA. (eMCS = emerged MCS; MCS = minimally conscious state; UWS = unresponsive wakefulness syndrome; SMA = supplementary motor area).

for the p value was again set to .001, and a cluster-level correction method (family-wise error rate correction) was applied. All resulting significant clusters ($p < .05$) were extracted, and by means of the automated anatomical labelling atlas-3 (AAL3) [36], the corresponding brain regions were identified.

2.8. Statistical Analysis. Further data processing steps were carried out using Excel [37] and jamovi [38]. Excel was used to create a general data overview and to sort the data, while jamovi was used for descriptive and quantitative data analysis. Frequency tables, contingency tables, and categorical tests were used to determine the extent of CCF in the different subgroups. Whenever the expected frequencies were

smaller than five and, thus, a central assumption of the chi-square test (χ^2) violated, Fisher's exact test statistic [39] was used instead. While the response rates are reported for all ROI analyses to compare the different approaches, the subsequent sections are limited to the one-tailed SVC analysis for reasons of clarity. Regarding the diagnostic questions of this paper, the Kruskal-Wallis tests (H) were used to assess possible differences between groups since the group sizes differed largely and, thus, were not suitable for parametric analyses. In addition, Spearman's rho (r_s) was applied as a nonparametric equivalent of the point-biserial correlation (r_{pb}) to measure the strength of the relationship between continuous and binary variables [40]. In cases where the association between two dichotomous variables

was to be investigated, Fisher's exact test was again applied since the condition of expected frequencies in more than 80.00% of the cells was not met here either.

For the first general prognostic analysis, the clinical evolution of the patients' diagnoses during their stay in the hospital was examined by means of frequency tables. Furthermore, based on the prognostic approach of Estraneo et al. [41], a hierarchical binary logistic regression model should first determine the goodness of various clinical factors (i.e., diagnosis at the time of fMRI assessment, age at onset of DoC, and aetiology of brain injury) for the prediction of the patient's outcome at the time of their discharge from hospital and, in a second step, measure the extent of incremental validity by adding the neuronal fMRI data (CCF).

For the WBA, in addition to a frequency table to determine the occurrence of significant whole-brain activations, relations to the clinical variables were also investigated by means of point-biserial correlations and chi-square tests. Moreover, the number of significant activations in the specific cluster regions was compiled in Microsoft Excel tables and manually assigned to superordinate brain regions in order to obtain an overview of areas that could also be involved in motor imagery tasks.

Randomization was not applicable for this study. CRS-R scores at the time of fMRI were obtained before the fMRI, and the analysis of fMRI data was standardized. No blinding could be obtained for the CRS-R assessment at discharge, as the same persons were responsible for CRS-R and fMRI assessments.

3. Results

3.1. Subjects. 73 patients (25 women) were enrolled in the study, the median age being 50 years (range = 15 – 85 years). At the time of the fMRI examination, 35 patients were diagnosed with UWS based on their CRS-R score, another 35 with MCS (6 MCS+, 29 MCS-), and three had already recovered consciousness (eMCS). There were 25 traumatic and 48 nontraumatic brain injury cases. The median time between the acquisition of the brain injury and the fMRI examination was two months (range = 0 – 264 months), and 77% of patients had their onset of DoC more than 28 days before the fMRI investigation. More detailed descriptive data for each patient can be found in the supplementary material (Table A1).

27 healthy controls (12 women) participated in the fMRI part of the study, all of whom had normal or corrected-to-normal vision, were native German speakers, and were between 21 and 68 years old (Mdn = 30 years).

3.2. ROI Analyses. The one-tailed SVC and ROI exploration analysis revealed significantly stronger activation during the tennis block in 25 of 27 healthy controls (93%). Besides, all three eMCS patients (100%) showed significantly stronger activations in all ROI analyses.

For the remaining 70 DoC patients, the response rate in the one-tailed SVC analysis was 10%. Table 1 provides an overview of the exact number and proportion of responders

according to diagnosis and type of ROI analysis. The higher activation rates of UWS patients in the two-tailed approaches are caused by 10 patients who showed significant but inverse activations (negative responders showed significantly more activation during rest than during the tennis paradigm; eight UWS, one MCS+, and one MCS-).

Figure 1 shows the neuronal activation pattern for one subject from each of the two control and patient groups during the tennis paradigm.

A right-sided Fisher exact test showed that the number of patients who were capable of CCF narrowly missed being significantly higher in MCS ($n = 6$) than in UWS ($n = 1$) patients ($p = .053$, OR = 7.03) for the one-tailed SVC data but revealed a significant association based on the data of the one-tailed ROI exploration analysis ($p = .042$, OR = 4.89), where the proportion of responders was significantly higher in MCS ($n = 8$) than UWS patients ($n = 2$). The same association was tested for significance with a chi-square test for the data of the two-tailed SVC analysis, but no significant differences between UWS ($n = 6$) and MCS ($n = 7$) patients were found ($\chi^2(1) = 0.09$, $p = .759$, OR = 1.21). For the two-tailed ROI exploration, no significant difference between UWS ($n = 8$) and MCS ($n = 9$) was found either ($\chi^2(1) = 0.08$, $p = .781$, OR = 1.17) with a chi-square test.

A Kruskal-Wallis test showed that the CRS-R scores of the seven responders of the one-tailed SVC approach (Mdn = 9.00) did not differ significantly from those of the 63 nonresponders (Mdn = 6.50, $H(1) = 3.13$, $p = .077$, $\epsilon^2 = .05$). However, the one-sided point biserial correlation revealed a significant relation between the binary variable CCF and the continuous variable CRS-R score ($r_{pb} = .21$, $p = .038$) indicating that CCF shares 4.4% of the variability in the CRS-R score.

Besides that, it was found that all seven responders of the one-tailed SVC approach had a nontraumatic aetiology, so the right-sided Fisher exact test, to test the prior assumption that CCF is more common in patients after traumatic than nontraumatic brain injury, was not significant ($p = 1.000$, OR = 0.11). Neither age at onset of DoC ($r_{pb} = -.13$, $p = .289$) nor age at the time of fMRI ($r_{pb} = -.13$, $p = .276$) was significantly correlated with the ability of CCF. Furthermore, the duration of DoC, measured in months from onset to fMRI assessment, was also not significantly correlated with the ability of CCF ($r_{pb} = .11$, $p = .364$). Finally, Fisher's exact test showed no significant differences for the frequency of CCF between patients tested before the adaption of the neuronal assessment procedure and those tested after ($p = 0.275$, OR = 0.469) or those tested before the change of MRI scanner and those tested after ($p = 0.476$, OR = 0.6).

At the time of their discharge from the hospital (Mdn = 6 months, range = 0 – 264 months), the majority of DoC patients ($n = 51$, 73%) had not changed their condition (29 of 35 UWS patients (83%), 22 of 35 MCS patients (63%). On the contrary, two patients diagnosed with UWS (6%) had recovered consciousness and four UWS patients (11%) improved to MCS-. Of the 13 MCS patients who changed their condition, eight regained consciousness

TABLE 1: Response rates during tennis paradigm in controls and DoC patients.

Diagnosis ^a	Responder	Type of ROI analysis			
		One-tailed SVC	Two-tailed SVC	One-tailed ROI Exploration	Two-tailed ROI Exploration
Controls (<i>n</i> = 27)	Yes	25 (92.60%)	24 (89%)	25 (93%)	23 (85%)
	No	2 (7.40%)	3 (11%)	2 (7%)	4 (15%)
eMCS (<i>n</i> = 3)	Yes	3 (100%)	3 (100%)	3 (100%)	3 (100%)
	No	0 (0%)	0 (0%)	0 (0%)	0 (0%)
MCS total (<i>n</i> = 35)	Yes	6 (17%)	7 (20%) ^b	8 (23%)	9 (26%) ^b
	No	29 (83%)	28 (80%)	27 (77%)	26 (74%)
MCS+ (<i>n</i> = 6)	Yes	0 (0%)	0 (0%)	0 (0%)	1 (17%) ^b
	No	6 (100%)	6 (100%)	6 (100%)	5 (83%)
MCS- (<i>n</i> = 29)	Yes	6 (21%)	7 (24%) ^b	8 (28%)	8 (28%) ^b
	No	23 (79%)	22 (76%)	21 (72%)	21 (72%)
UWS (<i>n</i> = 35)	Yes	1 (3%)	6 (17%) ^b	2 (6%)	8 (23%) ^b
	No	34 (97%)	29 (83%)	33 (94%)	27 (77%)

Note: responders are defined as subjects who showed significant different activations in the supplementary motor area during the tennis than during the rest phases. The values in round brackets indicate the proportion of responders and nonresponders in relation to all subjects in the respective diagnosis group. ^aThe diagnosis given at the time of the fMRI examination. ^bGroups that include “negative responders.” (DoC = disorder of consciousness; ROI = region of interest; SVC = small volume correction; eMCS = emerged from MCS; MCS = minimally conscious state; UWS = unresponsive wakefulness syndrome).

(23%, 2 MCS+, and 6 MCS-), 1 (3%) improved from MCS- to MCS+, while four deteriorated to UWS (11%, 1 MCS+, and 3 MCS-). The proportion of MCS patients who improved was not significantly higher than that of UWS patients ($\chi^2(1) = 0.76$, $p = .382$, OR = 1.67). Of the 15 patients who showed an improvement until discharge, 7 showed significant activations in one of the ROI analysis approaches. Four of those were inverse activations.

The outcome of patients at the time of discharge from hospital was divided into two categories according to the CRS-R: those who improved by one (UWS to MCS or MCS to eMCS), two (UWS to eMCS), or within a clinical state (MCS- to MCS+) were classified as improved ($n = 15$, 21%), and those who had the same diagnosis or had worsened compared to the time of the fMRI examination were identified as not improved ($n = 55$, 79%). The first model, which is composed of three clinical parameters discussed as relevant for outcome in DoC and which is presented in Table 2 A, could not predict the improvement of DoC patients better than the intercept model ($\chi^2(3) = 2.41$, $p = .491$, $R^2_N = .05$, AIC = 78.30). With a cut-off value of 0.25, this model identified 84% (specificity) of the patients who did not improve their condition, while it only classified 33% (sensitivity) of the patients who improved correctly (AUC = .66). The investigation of the contingency table that contained all predictors of the second model (cf. Table 2 B) revealed that expected values were equal to zero in nine cases and thus indicative of incomplete information from the neuronal predictor CCF. Hence, the model did not provide a useful prediction for the outcome of the patients ($\chi^2(4) = 2.66$, $p = .616$, $R^2_N = .06$, AIC = 80.01).

Moreover, the CRS-R scores at the time of discharge from the hospital were compared between responders (Mdn = 9) and nonresponders (Mdn = 7) based on a

Kruskal-Wallis test which showed that they did not differ significantly ($H(1) = 1.63$, $p = .202$, $\epsilon^2 = .02$). Furthermore, a one-sided point biserial correlation supported these results by also showing no significant positive association between the ability of CCF and the CRS-R score at the time of hospital discharge ($r_{pb} = .15$, $p = .102$).

3.3. Whole-Brain Analysis. Based on the one-tailed SVC data, 28 DoC patients (40%) showed significant activations in regions outside the SMA, the number of significant clusters ranging from one to 16 (Mdn = 2). When using the data from the two-tailed SVC analysis, this proportion was even higher ($n = 35$, 50%), and the upper limit of significant clusters rose to 23 (Mdn = 3).

Significant associations between the presence of activated brain clusters outside the ROI and clinical variables were not found for aetiology ($\chi^2(1) = 0.00$, $p = 1.000$, OR = 1.00), age at onset of DoC ($r_{pb} = -.02$, $p = .896$), CRS-R score at the time of fMRI ($r_{pb} = .20$, $p = .104$) or duration of DoC ($r_{pb} = .10$, $p = .422$). Besides, there was no significant correlation between the whole-brain activations and patients' outcome at the time of discharge from the hospital ($\chi^2(1) = 0.13$, $p = .714$, OR = 0.80). However, a chi-square test showed that the probability of significant activations outside of the ROI was more than three times higher for MCS patients compared to UWS patients ($\chi^2(1) = 5.95$, $p = .015$, OR = 3.43).

Matching the significant clusters with the underlying brain area names based on the AAL3 resulted in 693 significant activations that could be assigned to underlying areas. Of those, 392 (57%) were in the left hemisphere and 287 (41%) in the right. The remaining 14 (2%) were attributed to the vermis and, thus, not to any specific hemisphere. In

TABLE 2: Hierarchical binary logistic regression for improvement at time of discharge from hospital.

Predictor	Estimate ^a	95% CI for estimate		SE	z	p	OR ^b	95% CI for OR		
		Lower	Upper					Lower	Upper	
Step 1										
	Intercept	-1.61	-3.59	0.38	1.01	-1.58	0.114	0.201	0.03	1.47
A	Age at onset	-0.01	-0.04	0.03	0.02	-0.42	0.673	0.99	0.96	1.03
	Aetiology ^c	0.76	-0.46	1.97	0.62	1.22	0.223	2.13	0.63	7.17
	Diagnosis at fMRI ^d	0.69	-0.52	1.91	0.62	1.12	0.265	2.00	0.59	6.74
Step 2										
	Intercept	-1.52	-3.53	0.49	1.03	-1.48	0.139	0.22	0.03	1.64
B	Age at onset	-0.01	-0.04	0.03	0.02	-0.46	0.645	0.99	0.96	1.03
	Aetiology ^c	0.68	-0.56	1.92	0.63	1.08	0.282	1.98	0.57	6.83
	Diagnosis at fMRI ^d	0.74	-0.49	1.97	0.63	1.19	0.236	2.10	0.62	7.16
	CCF	-0.57	-2.87	1.74	1.18	-0.48	0.631	0.57	0.06	5.71

Note: model A is composed exclusively of clinical predictors, while model B also includes covert command following (CCF). None of the predictors from either model is a significant predictor of patients' outcome at the time of hospital discharge ($p > .05$). ^aEstimates represent the log odds of improvement occurred vs. improvement did not occur. ^bOR refers to odds ratio, a common effect size for categorical data. ^cAetiology: traumatic vs. nontraumatic. ^dDiagnosis at fMRI: minimally conscious state vs. unresponsive wakefulness syndrome in functional MRI.

addition, there were 129 further significant clusters that could not be clearly classified by SPM12 using the labels of the AAL3. Table 3 lists all regions by their frequency of significant activations based on the one-tailed SVC data.

4. Discussion

This study revealed that (i) nontraumatic patients can display CCF, (ii) that some patients show negative responses, and (iii) that WBA activations are more likely in MCS than UWS patients, while confirming former study results on CMD and comparing different fMRI analysis strategies.

4.1. ROI Analysis. The proportion of patients who displayed CCF in the tennis paradigm was determined. Seven of 70 DoC patients (10%) showed significant activation in the SMA using the most restrictive approach (one-tailed SVC). Therefore, the response rates found in Monti et al. (approx. 9%) [26] and Kondziella et al. (5-15%) [16] could be replicated for this sample. Even though the proportion of responders in the group of healthy controls was not 100% as in Boly et al. [42], 93% of the controls showed CCF during the tennis paradigm, which is comparable to Bodien et al. [28] or even higher than the proportion reported in more recent CCF studies [21, 43, 44]. Furthermore, the fact that all three eMCS patients showed CCF also confirms the usefulness of the tennis paradigm to measure voluntary cognitions. Hence, the results for the control groups confirm the high specificity of the motor imagery task, which has previously been highlighted as a strength [16, 26, 42].

While the response rate for the eMCS patients was 100% for all ROI approaches, the one-tailed analyses were slightly more sensitive than the two-tailed approaches for the healthy controls. For the MCS patients, the ROI exploration approaches were the most sensitive. Interestingly, the six MCS+ patients did not show significant activations (except

for one patient who showed a “negative response” in the two-tailed ROI exploration), although they were able to follow commands at the bedside evaluation. However, of the MCS- patients, who showed no bedside command following, 28% showed significant activations in the ROI exploration approach. The largest differences were found in UWS patients; the response rates of the two-tailed analysis were multiple times higher than for the one-tailed analysis. It was found that ten patients behaved in a hypothesis-incongruent manner by showing stronger activations in the SMA during rest than in tennis. Interestingly, of the eight UWS “negative responders,” three improved to MCS by the time they were discharged (38%), and thus, the proportion of improved “negative responders” in UWS was twice as high as in the total sample of UWS patients (17%). Of the two MCS “negative responders” (1 MCS+, 1 MCS-), the patient in MCS- improved. Since all studies to date are based on one-tailed t -contrasts [25, 26, 42, 45] or do not clearly differentiate between one- and two-tailed results [29, 46, 47], it is not possible to compare this finding with previous research. Therefore, and because this finding only applied to a small subgroup of patients, no reliable conclusions can be drawn yet. However, it is a novel observation that requires further research to clarify the underlying factors. Possible explanations for the “negative responders” are that they either took longer to implement the tennis instruction—as was already demonstrated for stroke patients [48]—so that the tennis and rest phases overlapped, or they thought about movements during the rest phases causing a significant activation of the SMA as well [49, 50]. Another possible explanation could be movement artefacts during the rest phases [51].

Overall, the two one-tailed approaches showed an overall high agreement in most cases, although the sensitivity of the one-tailed ROI exploration analysis was slightly higher. Equally important, it was shown that the two-tailed

TABLE 3: Activated brain areas outside the supplementary motor area during motor imagery.

Activated brain areas	Left hemisphere (LH) activations	Right hemisphere (RH) activations	LH+RH activations	% of all activations
Frontal gyrus	129	94	223	32.2%
Superior frontal gyrus	33	27	60	8.7%
Cingulate cortex	26	22	48	6.9%
Inferior frontal gyrus	19	18	37	5.3%
Middle frontal gyrus	22	12	34	4.9%
Precentral gyrus	20	11	31	4.5%
Orbital gyrus	6	2	8	1.2%
Gyrus rectus	3	2	5	0.7%
Parietal gyrus	78	55	133	19.2%
Postcentral gyrus	21	13	34	4.9%
Precuneus	17	14	31	4.5%
Supra marginal gyrus	13	11	24	3.5%
Inferior parietal gyrus	15	7	22	3.2%
Superior parietal gyrus	12	10	22	3.2%
Temporal gyrus	50	51	101	14.6%
Middle temporal gyrus	15	10	25	3.6%
Superior temporal gyrus	7	15	22	3.2%
Temporal pole	9	9	18	2.6%
Inferior temporal gyrus	10	2	12	1.7%
Fusiform gyrus	4	5	9	1.3%
Heschl's gyrus	2	6	8	1.2%
Parahippocampal gyrus	1	2	3	0.4%
Amygdala	1	1	2	0.3%
Hippocampus	1	1	2	0.3%
Occipital gyrus	63	35	98	14.1%
Middle occipital gyrus	16	8	24	3.5%
Superior occipital gyrus	15	8	23	3.3%
Cuneus	12	8	20	2.9%
Calcarine fissure	9	8	17	2.5%
Lingual gyrus	5	3	8	1.2%
Inferior occipital gyrus	6	0	6	0.9%
Cerebellum	25	17	56 ^a	8.1%
Vermis	—	—	14	2%
Basal ganglia	7	5	12	1.7%
Putamen	4	3	7	1%
Caudate nucleus	3	1	4	0.6%
Pallidum	0	1	1	0.1%
Angular gyrus ^b	11	12	23	3.3%
Rolandic operculum ^b	10	8	18	2.6%
Paracentral lobule ^b	12	4	16	2.3%
Insula ^b	6	5	11	1.6%
Locus coeruleus ^b	1	1	2	0.3%
Total activations	392	287	693 ^a	100%

Note: shown are areas of the brain where there was more activation during tennis than during rest periods based on the one-tailed small-volume correction contrast data. The areas are listed according to the frequency of their activation. ^aTotal is higher than the sum of the LH and RH activations, as the 14 vermis activations are included. ^bBrain areas that could not be clearly assigned to any of the superordinate areas.

ROI analysis can uncover hypothesis-incongruent cases for which it should be clarified in the future whether they are caused by chance or due to specific factors and how this relates to diagnostic and prognostic variables.

Only patients with nontraumatic brain injury showed CCF, which is in contrast to all previous studies [16, 26, 29, 52]. One explanation could be that the proportion of nontraumatic patients in this study was almost twice as high as in the study of Monti et al. (66% vs. 39%) [26]. Moreover, only severe traumatic cases spent a longer time in hospital, while milder traumatic cases recovered and were discharged early, receiving no fMRI. However, this study provides clear evidence against the view of Byrne and Hardiman [53], who joined Monti et al. [26] in saying that wilful consciousness is exclusive to patients suffering from DoC due to a traumatic aetiology.

Even though responders did not differ significantly from nonresponders regarding their CRS-R score at the time of fMRI examination, the point-biserial correlation revealed a significant relation between the two variables and thus points in the same direction as the study by Schnakers et al. [52], which found higher CRS-R total scores in responders compared to nonresponders. The finding that MCS patients were more likely to neurally follow commands than UWS patients based on the one-tailed ROI exploration data is not only consistent with the results of Kondziella et al. [16] and Schnakers et al. [52] but also with the observation that the ROI exploration approach is more sensitive than the SVC approach, since the latter was scarcely not significant, although the odds ratio in both cases indicated a strong practical effect. Neither age at onset of DoC nor age at time of fMRI examination was significantly related to the performance in the CCF task. Moreover, the duration of DoC was also not a significant correlate of the CCF ability. These three findings are consistent with those of previous studies [30, 45, 52].

To answer the diagnostic question, the tennis fMRI paradigm is a useful tool in identifying CMD but the exact methods of analysing the data have to be investigated further and standardized.

Neither age at onset of DoC, nor the aetiology of the brain injury, or the diagnosis at the time of fMRI examination was a significant clinical predictor of improvement at the time of discharge from the hospital. Thus, the findings are in line with those of an older study [54] which also failed to identify any clinical factors as useful prognostic indicators for the recovery of DoC patients. Even in more recent studies, the three clinical factors (age [55–57], aetiology [41, 55, 58], and clinical state [41]) could not always be replicated as influential predictors of outcome in DoC patients. Due to possible interactions between the different predictors, it is difficult to formulate causal explanations for the lack of prognostic effects [56]. Nevertheless, the lack of influence of aetiology on the outcome could be because the cause of DoC lost its influence on the patients' chance to recover in the chronic phase [58]. Furthermore, Kotchoubey and Pavlov [59] showed that the initially significant predictor diagnosis lost its influence on prognosis when, instead of recovering consciousness, only the improvement to the next

higher clinical state was selected as outcome. Moreover, the three predictors of the clinical prognostic model could possibly be spurious correlates of further unconsidered factors and thus mask true associations. Accordingly, Lanzillo et al. [60] attribute the better outcome of traumatic compared to nontraumatic patients in their study not primarily to their aetiology, but rather to their associated lower number of comorbidities and younger age. Finally, the prognostic power of the clinical predictors was investigated only for the total sample of DoC patients and not separately for the two diagnostic subgroups as in Steppacher et al. [61], who found reliable prognostic predictors exclusively for UWS but not for MCS patients.

Due to the small proportion of responders compared with nonresponders in this study, the available data were not sufficient to include the ability of CCF as a reliable predictor in the logistic regression model; thus, more observations are needed. However, based on the Kruskal-Wallis test and the point-biserial correlation, the positive effect of the CCF ability for the patients' recovery [25, 30] was not confirmed for this sample since responders neither had significantly higher CRS-R scores nor did they improve more often by the time of their discharge from hospital compared to nonresponders. Edlow et al. [43] found no significant association between the performance in a motor imagery fMRI task in acute DoC patients and their scores in the Glasgow outcome scale—extended at a 6-month follow-up. Kotchoubey and Pavlov [59] concluded that patients' responses to stimulation in fMRI were one of the poorest predictors of improvement, and Vogel et al. [45] confirmed the predictive power of the tennis paradigm only for the outcome of UWS but not MCS patients. As with the clinical predictors, specifying exact causal factors for the lacking predictive effect of motor imagery in this study is not possible.

To answer the prognostic question, no prognostic value could be found comparing the outcome of CMD patients with and without DoC.

4.2. Whole-Brain Analysis. The finding that 40% of DoC patients showed significantly stronger activations somewhere in the brain during the imagination than during rest confirms that neuronal processing is possible in principle in a substantial proportion of DoC patients.

No differences in the level of whole-brain activations were found between patients with traumatic vs. nontraumatic brain injury but between MCS and UWS patients. The fact that MCS patients were three times more likely to display whole-brain activations than UWS patients is an important observation for differential diagnosis of DoC. However, beyond this, the whole-brain activations did not show significant associations with the other variables. In contrast to Bardin et al. [62], the diagnostic power of the WBA could only be classified as comparable to, but not better than the ROI analysis since both approaches only showed significant associations with the clinical state of patients to a similar extent (OR = 3.43 for WBA, OR = 4.89 for ROI). Although there are already some studies in the field of DoC that rely on whole-brain data, so far, they only involve

the analysis of resting-state activation [63, 64], the development of neurobiologically realistic models [65], and so-called brainnetome networks [66]. Hence, this is, to our knowledge, the first detailed analysis of whole-brain activations during an active fMRI paradigm, so the results reported here cannot yet be compared with other findings. Instead, they pave the way for further analyses of the whole brain activations of DoC patients to identify more robust diagnostic and prognostic markers.

Based on visual inspection, a difference in the activation frequency of the two hemispheres became apparent as there was more activation in the left than the right hemisphere. This is in line with Sabaté et al. [48] and Stinear et al. [67], who found a general dominance of the left hemisphere for motor imaginations.

New research questions arise based on the identified activated areas, especially since 16 of the 37 classified regions (43%) were more frequently activated than the SMA. One research idea might be to define the ROI not as a single region but as a network of diverse regions for which motor imagination involvement has been demonstrated. Although this may be accompanied by a loss of the benefits of the ROI approach [68], there might be new advantages for the diagnosis and prognosis of DoC patients.

4.3. Limitations. Besides the general disadvantages of active fMRI paradigms (risk of high false-negative rate and thus low sensitivity [16]; higher time and financial costs than behavioural/EEG assessments [69]), there are also study-specific limitations. First, despite its comparatively large sample size, the patient sample might not be representative of DoC patients due to the known exclusion criteria of an MRI examination. These had the consequence that only patients who were neither dependent on external respiration nor had extensive spasticity or strong body movements could be analyzed. Since fMRI examinations are time-consuming, expensive, and also stressful for the patients, only a single scan of each patient could be included, although DoC patients are often subject to fluctuations of vigilance [43, 70] and a single fMRI assessment may miss vigilant moments. Moreover, the average attention span of DoC patients is less than ten minutes and thus might be not sufficient for completing the tennis paradigm which lasted approximately ten minutes [71]. Besides, the use of different scanners and the adaption of the tennis paradigm may have affected the study results. Even though there were no significant differences for the frequency of CCF between patients tested before the adaptations and those tested after, retrospectively, the equivalence of the procedures can no longer be proven. Moreover, as Wannez et al. showed, a single CRS-R score can lead to a high amount of misdiagnosis compared to repeated examinations [72], and although our examinations were done weekly, a higher frequency would likely have improved our diagnostic accuracy. Furthermore, it can be criticized that the observed period was too short to make reliable predictions. Moreover, the time at which patients were discharged from the hospital varied for each patient, which reduces the comparability between patients. In addition, there were no data available on some clinical

parameters considered relevant in previous research (medication [73–75]; comorbidities [76–78]).

The level of sensitivity of the fMRI paradigm could also influence the results. Even though fMRI methods, compared to solely behavioural assessments, can detect patients with CMD [79], the sensitivity of active paradigms is still lower compared to passive and resting-state approaches [16]. This is not only true for DoC patients who are frequently subject to attentional and arousal fluctuations [43, 45, 74, 79] or have specific other deficits that limit task processing [26, 45, 74] but also for healthy control subjects [21, 43, 44] since it is a very demanding task that requires many cognitive skills at the same time [26]. Thus, it is important to emphasize that just because patients did not show CCF in one fMRI examination, this does not mean that they are not conscious, nor that their current condition cannot improve in future [27, 43, 79, 80]. For clinical practice, this results in the dilemma of constant balancing between the two ends of the specificity-and-sensitivity-continuum. While Vogel et al. [45] see the priority of fMRI as a prognostic tool in the avoidance of false-positive findings in order not to raise false hopes among relatives, the focus of the majority of researchers is to overlook as few patients with CMD as possible [26, 27].

Three final limitations relate to the statistical analyses. For the prognostic questions, a dichotomous outcome variable was chosen because the assumptions for building a multinomial logistic regression model were not fulfilled. This naturally results in a loss of information compared to a multilevel outcome variable. Moreover, for reasons of clarity, the specific whole-brain areas of the WBA identified by means of the AAL3 were combined manually into superordinate areas. Besides the reduced reproducibility, some areas could be grouped less (e.g., insula) than others (e.g., cerebral lobes), which influences the interpretability of the respective activation frequency. Finally, parts of our analyses were explorative (search for associations between significant activations and clinical factors, whole-brain analysis) and, therefore, do not exhibit enough power to draw exact conclusions but rather should be used to form concrete hypotheses for future studies.

5. Conclusion

Based on one of the largest fMRI datasets available to date in the field, this study set out to validate previous study findings in relation to diagnosis and prognosis in people with DoC. 10% of the patients displayed CCF indicative of CMD. In contrast to all previous research, only nontraumatic patients showed CCF and some patients showed inverse activation patterns of the SMA, but the significance of this has to be further investigated. No other significant associations were found between clinical variables and the ability of CCF for diagnosis and prognosis. The tennis paradigm proved useful for identifying CMD in DoC patients but the diagnosis did not provide any advantages for short-term prognostics. The one-tailed ROI exploration analysis showed higher sensitivity in the assessment of CCF compared to the one-tailed SVC analysis, while the two-tailed approaches

were useful for the identification of hypothesis-incongruent cases. The WBA not only showed that multiple brain areas are activated during motor imagery tasks in a considerable amount of patients but also that MCS patients are more likely to show these activations.

Abbreviations

CMD: Cognitive motor dissociation
 CRS-R: Coma recovery scale-revised
 DoC: Disorder of consciousness
 FA: Flip-angle
 fMRI: Functional MRI
 FOV: Field-of-view
 MCS: Minimally conscious state
 CCF: Covert command following
 ROI: Region of interest
 SPM: Statistical parametric mapping
 SVC: Small volume correction
 TE: Time-to-echo
 TR: Time of repetition
 UWS: Unresponsive wakefulness syndrome
 WBA: Whole brain analysis.

Data Availability

Data that support the findings of this study are available in the supplementary material. The raw MRI data are not publicly available due to privacy and ethical restrictions and as this was not approved by the local ethics committee for this potential sensitive data. Contrast images reflecting significantly more activity for the tennis compared to the rest condition are available by request from the authors and after approval of such requests by the local ethics committee.

Ethical Approval

The study was conducted according to the principles of the Declaration of Helsinki and approved by the local ethics committee in Salzburg (No: 1148/2021).

Conflicts of Interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or nonfinancial interest in the subject matter or materials discussed in this manuscript.

Authors' Contributions

MK, LS, VS, ET, and JB contributed to the study conception and design, and MK, LS, VS, JC, and JB performed material preparation and data collection. Data analysis was conducted by VS, LS, and MK, and all authors contributed to the interpretation of the data. Supervision was provided by MK, LK, and ET, and project administration was done by LS and VS. The first draft of the manuscript was written by VS and LS, and all authors commented on previous versions of the manuscript. All authors read and approved

the final manuscript. Laura Schnetzer and Verena S. Schätzle contributed equally to this work.

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Supplementary Materials

The supplementary material contains Figure A1 showing the supplementary motor area mask and Table A1 containing more detailed information of all patients included in the study. (*Supplementary Materials*)

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